
Histological Clues in Interpreting Vulvar Inflammatory and Autoimmune Dermatoses

2

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Introduction

This chapter will be structured in the following manner. A specific histological term that may provide a diagnostic clue will be precisely defined. Along with the histological definition, the clinical correlate will be described so that there is the beginning of the essential clinicopathologic correlation that is always necessary in order to make the best possible diagnosis. After presenting this information, the reader will be introduced to a brief discussion of some of the entities in which such histological changes might be observed. This presentation is not meant to be comprehensive, and certainly, not every situation in which one might encounter the histological change will be addressed. Rather, the intent is to provide a quick overview of the most common situations in which each finding might be identified when examining tissue from the vulva. Finally, we will discuss additional features that one might consider when observing the histological change that would enable for a more precise resolution of the differential diagnosis.

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Histological Clues

Spongiosis

Spongiosis is defined as the presence of intraepidermal edema. Microscopically, this manifests as an increased space between adjacent keratinocytes and widening of intercellular spaces on routine sectioning (Fig. 2.1). In more florid cases, there may be loculations of fluid accumulation either within the epidermis or in the overlying stratum corneum. Clinically, spongiosis presents as eczematous dermatitis. This is an “oozing,” wet eruption that may also present with maceration in the vulva. In a very acute process, there will be no change in the stratum corneum. However, as the process becomes more subacute or chronic, there is almost always parakeratosis. Long-standing lesions almost always demonstrate acanthosis. Spongiosis may be seen in the posttraumatic state wherein hemorrhage may be present. There is a wide range of spongiotic (eczematous) conditions that occur in the vulva, including irritant or allergic contact dermatitis, an id reaction and secondary to dermatophyte infections. The specific features useful to distinguish between these entities can be found in Chap. 3. For example, the presence of necrotic keratinocytes would suggest irritant contact dermatitis, whereas Langerhans cell microabscess would suggest allergic contact dermatitis.

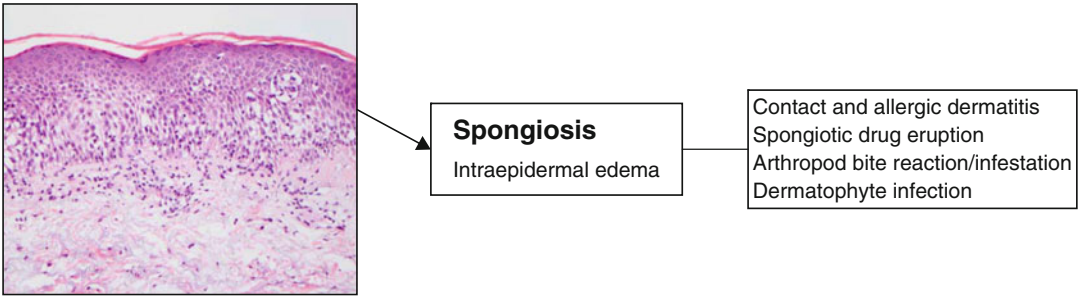


Fig. 2.1 Spongiotic pattern. Spongiosis is characterized by intraepidermal edema

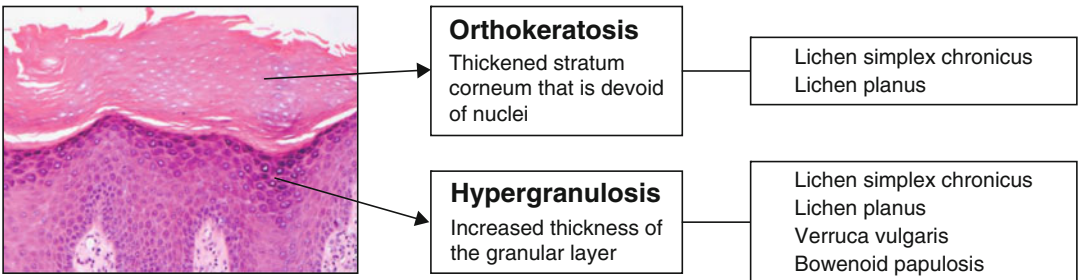
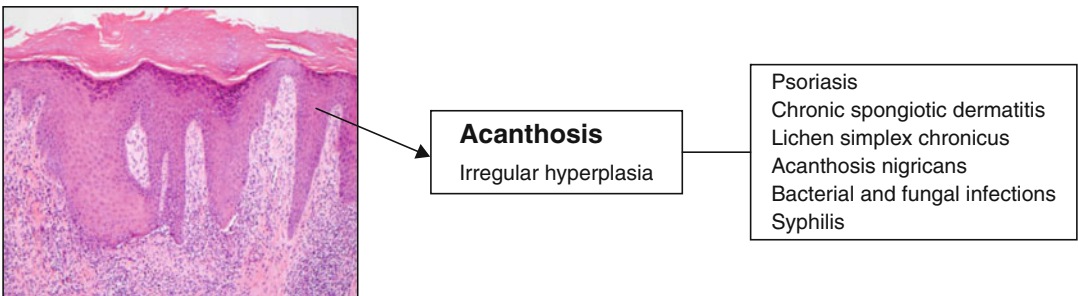


Fig. 2.2 Acanthotic pattern is characterized by irregular epidermal hyperplasia

Acanthosis

Acanthosis is defined as a thickened epidermis. Acanthosis may be “regular” with rete ridges of similar length (resembling psoriasis) or “irregular” with rete ridges with marked difference in length and width such as what is seen in pseudoepitheliomatous hyperplasia (Fig. 2.2). The clinical correlation of acanthosis is the sense of thickening of the skin upon palpation. Acanthosis is frequently associated with changes

in the stratum corneum such as parakeratosis or orthokeratotic hyperkeratosis. Acanthosis is evidence of chronicity and does not occur in the acute setting. Thus, one may think of plaque-stage psoriasis that has been present for a while when there is regular acanthosis. This finding would not be expected in a relatively acute lesion of psoriasis. In addition, psoriasis of the genital site can exhibit spongiosis and only focal mounds of parakeratosis containing neutrophils. Similarly, chronic spongiotic (eczematous) processes will

demonstrate regular acanthosis, though acute spongiotic processes will not show this change. Lichen simplex chronicus may show either regular or irregular acanthosis, and this always occurs with hypergranulosis and orthokeratotic hyperkeratosis as well as vertical papillary dermal fibrosis. In acanthosis nigricans, there is frequently regular acanthosis. Regular (psoriasiform) acanthosis is a common feature of syphilis, and in these cases plasma cells are almost always seen in the inflammatory infiltrate. Many other infectious diseases including viral, bacterial, and fungal infections demonstrate irregular acanthosis, and most commonly, there is a brisk inflammatory infiltrate in these cases.

Psoriasiform Hyperplasia

See regular acanthosis above.

Parakeratosis

Parakeratosis is the preservation of nuclei into the stratum corneum (Fig. 2.2). The clinical correlate of parakeratosis is the presence of a superficial scale. Lesions that demonstrate parakeratosis are invariably described as scaly processes. This finding occurs in two basic types of conditions. It may be seen with abnormal maturation of keratinocytes such as what may be seen in squamous cell carcinoma, vulvar intraepidermal neoplasia (VIN), or bowenoid papulosis. It may also be seen in hyperproliferative states such as psoriasis and spongiotic dermatitis and with infectious processes. The observation of cytological atypia would point the diagnostician in the direction of a condition with abnormal maturation, while the presence of spongiosis and/or neutrophils might be helpful in pointing one toward a diagnosis of a spongiotic process or toward psoriasis.

Orthokeratotic Hyperkeratosis

Hyperkeratosis is defined as the excess stratum corneum for the site. Orthokeratosis describes the

case when the excess keratin is devoid of nuclei (unlike parakeratosis). The excess keratin may demonstrate a basket-weaved pattern or may be compact (Fig. 2.2). The clinical correlate is that of a scale that may demonstrate a brownish color when the orthokeratosis is marked in extent. Orthokeratotic hyperkeratosis is most commonly encountered in lichen simplex chronicus and is often a clue to chronic irritation or rubbing. This is especially true when the basket-weaved pattern is lost and there is compaction of the stratum corneum. Despite the atrophic epidermis that characterizes well-developed lesions of lichen sclerosus, the stratum corneum tends to be hyperkeratotic and orthokeratotic in this condition. The difference in the thickness of the epidermis (acanthotic vs. atrophic) can be a useful additional clue to distinguish lichen simplex chronicus from lichen sclerosus, although one can see superimposed changes of lichen simplex chronicus in long-standing lichen sclerosus due to rubbing.

Hypergranulosis

Hypergranulosis is defined as a relative increase in the thickness of the granular layer (Fig. 2.2). This is site specific and one would expect to see a much thicker granular layer on acral skin than is normal on vulvar skin. Hypergranulosis often correlates with a whitish color clinically. Depending upon the extent of the hyperkeratosis, the white coloring may be focal and “lacy” (lichen planus) or diffusely white (some cases of lichen simplex chronicus). When the observer notes hypergranulosis, several diagnostic entities become likely. Lichen simplex chronicus demonstrates this finding in concert with psoriasiform epidermal hyperplasia, compact orthokeratotic hyperkeratosis, and dermal fibrosis. In lichen planus, one sees hypergranulosis accentuated in eccrine acrosyringium along with a lichenoid inflammatory infiltrate. A verruca vulgaris may demonstrate hypergranulosis and frequently papillomatosis. If cytological atypia is noted, bowenoid papulosis should be considered as a diagnostic possibility.

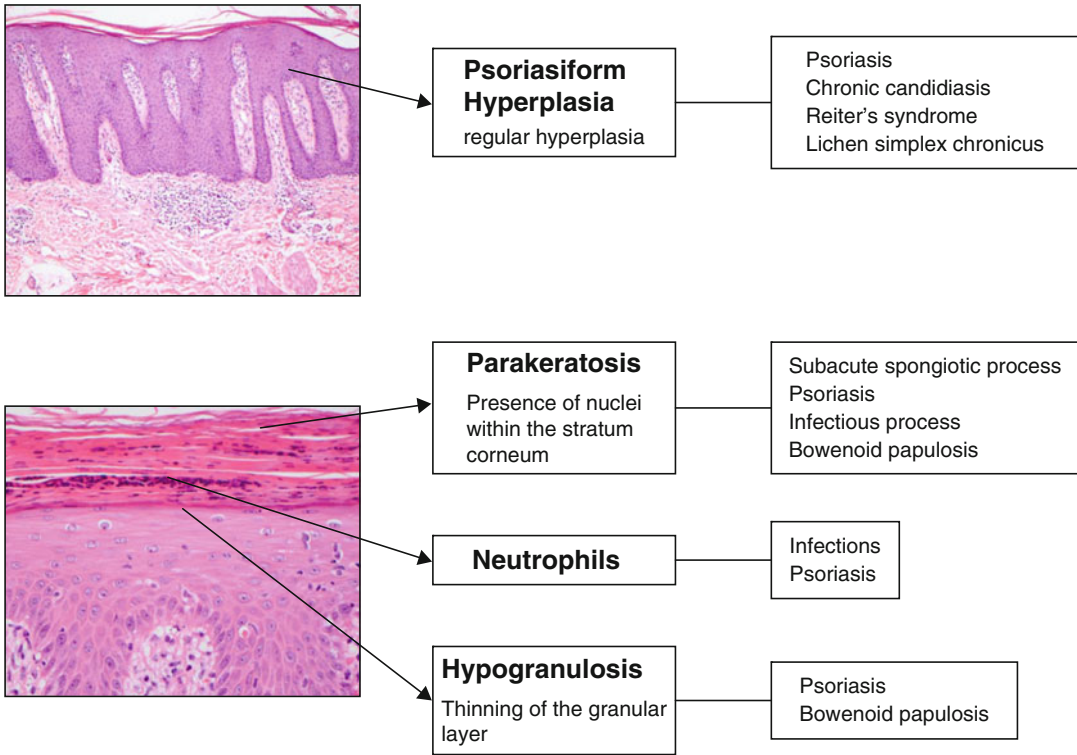


Fig. 2.3 Psoriasiform pattern is characterized by regular epidermal hyperplasia

Hypogranulosis

Hypogranulosis is defined as a relative thinning of the granular layer (Fig. 2.2). In some cases, it may be completely absent. Hypogranulosis frequently occurs in concert with parakeratosis. There is no reproducible clinical correlation to the observation of hypogranulosis. The most common situations where the observation of hypogranulosis is encountered in vulvar biopsies include psoriasis, relatively acute spongiotic dermatitis, and bowenoid papulosis. The presence of neutrophils may point toward the diagnosis of psoriasis, while the presence of spongiosis (see below) might lead to a diagnosis of some type of spongiotic (eczematous) process. Cytological atypia in the presence of hypogranulosis might favor a diagnosis of bowenoid papulosis.

Dyskeratosis

Dyskeratosis refers to the abnormal keratinization of individual cells within the lower portions or midportions of the epidermis (Fig. 2.3). This change may occur in situations with abnormal keratin production or in situations with exocytosis of lymphocytes into the epidermis. There is no clinical correlate to this finding except when it is extensive and may give rise to small vesicles. Dyskeratosis is a prominent finding in Darier's disease and in warty dyskeratoma. In both cases, there is also a prominent hyperkeratosis. Warty dyskeratoma will demonstrate a cup-shaped architecture that is not seen in Darier's disease. Dyskeratosis may be seen in inflammatory entities such as lichen planus in concert with hypergranulosis, orthokeratotic hyperkeratosis, and a

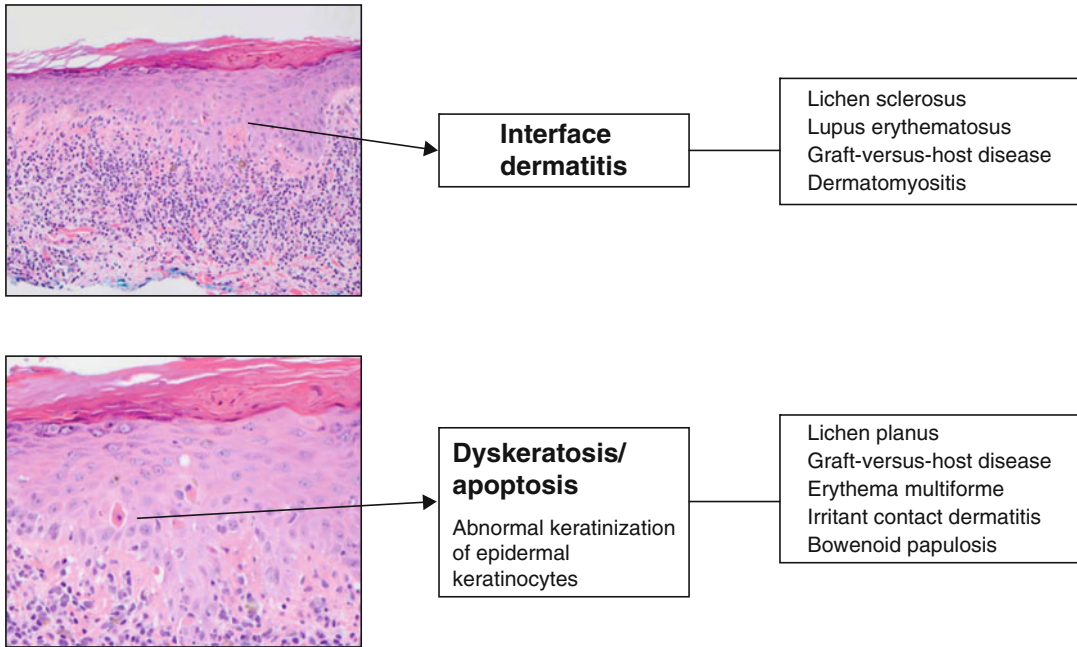


Fig. 2.4 Interface pattern is characterized by dyskeratotic or apoptotic keratinocytes

band-like inflammatory infiltrate. Similarly, dyskeratotic cells may be seen in erythema multiforme and in graft-versus-host disease, though the inflammatory infiltrate is not usually as pronounced as that seen in lichen planus. Cases of bowenoid papulosis may similarly demonstrate dyskeratosis and cytological atypia that is more diffuse than what is encountered with chemotherapeutic changes.

basal keratinocytes and melanocytes, namely, lichenoid or interface dermatoses, as described above. It is not associated with the acute onset of an inflammatory process, but rather, it is seen as a consequence of a process that has evolved over weeks to months. It can be seen as a secondary phenomenon in each of the diseases listed above in lichenoid and interface dermatitides and is most clinically apparent and concerning in darker-skinned individuals.

Pigment Incontinence

Pigment incontinence refers to the drop of melanin pigment from the basal layer of the epidermis into the papillary dermis where it is most commonly engulfed by macrophages (Fig. 2.4). When pigment incontinence is seen under a microscope, the clinicians can almost always detect anomalies in pigment distribution on the skin surface. This may result in an appearance of clinical hyperpigmentation or hypopigmentation, and the clinical difference is not always readily apparent microscopically. Pigment incontinence occurs in situations where there is destruction of

Sclerosis

Sclerosis is the deposition of dense fibrous tissues within the papillary dermis that is usually characterized by the presence of wispy type III collagen fibers. Sclerosis manifests clinically as hardening of the skin and the appearance and feel of a plaque. It occurs in chronic inflammatory processes. Linear, horizontally oriented sclerosis is a hallmark feature of well-developed lesions of lichen sclerosus. It occurs concomitantly with atrophying of the epidermis and overlying orthokeratotic hyperkeratosis. In general, the more

prominent the sclerosis, the less intense the inflammatory infiltrate and the older the lesion. Sclerosis can also be seen in morphea or scleroderma; however, these cases are extremely unusual in this location, and the sclerosis is not limited to the papillary dermis but is mainly centered within the reticular dermis. A lymphoplasmacellular inflammatory infiltrate may be present in these situations. Lichen simplex chronicus also demonstrates dermal fibrosis, but in most cases, the thickened dermal collagen is present in vertical columns within the papillary dermal tips and not in a horizontal array such as what is encountered in lichen sclerosis.

Neutrophils

Neutrophils, also known as polymorphonuclear leukocytes, are white blood cells that do not normally reside in the skin but migrate into the dermis and epidermis in a variety of inflammatory conditions. When present in clusters within the epidermis (most commonly the stratum corneum) (Fig. 2.2), the clinical appearance is that of pustules, vesicles filled with “cloudy” fluid comprised of serum and neutrophils. When not in the stratum corneum, epidermal pustules may present with painful erythema. Similarly, clusters of dermal neutrophils will be erythematous and are often associated with clinical pain. Neutrophilic abscesses within the stratum corneum and the epidermis are a common feature of psoriasis. Regular psoriasiform acanthosis, parakeratosis, hypogranulosis, and vascular ectasia occur along with the neutrophilic infiltrates. Neutrophilic abscesses in the outflow tract of follicular units may be a clue to seborrheic dermatitis. In the absence of other changes, neutrophilic abscesses occurring with scattered dermal eosinophils raise the possibility of acute generalized exanthematous pustulosis. Amicrobial pustulosis of the folds may also demonstrate subcorneal neutrophilic abscesses. As with other body sites, the presence of neutrophils within a biopsy should raise the possibility of an infectious process. When purely dermal, the presence of neutrophils should prompt the search for leukocytoclastic

vasculitis, Sweet’s syndrome, linear IgA bullous dermatosis, and cellulitis.

Plasma Cells

Plasma cells are a subtype of B lymphocyte that is normally present in mucosal regions. Their presence in the vulva is not unexpected, and they may reside there normally in small numbers. There is no clinical correlation to the presence of scattered dermal plasma cells. Conditions in which increased plasma cells may be present include syphilis that also demonstrates psoriasiform epidermal hyperplasia and a band-like inflammatory infiltrate. Plasma cell vulvitis would have abundant dermal plasma cells as well as erythrocyte extravasation and hemosiderin deposition. A subacute folliculitis can result in the appearance of scattered plasma cells along with abundant lymphocytes and neutrophils. In lesions of lichen sclerosis, scattered plasma cells may be encountered, but the characteristic changes as described above will be detected. Plasma cells are also frequently encountered in connective tissue diseases such as lupus erythematosus, morphea, and scleroderma. These cells will be present along with the changes as described earlier in the chapter and in subsequent chapters.

Acantholysis

Acantholysis is the dyscohesion of adjacent keratinocytes caused by the dissolution of desmosomes (Fig. 2.5). This gives the microscopic appearance of an epidermis that is “falling apart.” Acantholysis usually occurs within the stratum malpighium, though similar changes can occur in the stratum granulosum. There is often associated spongiosis in situations that give rise to acantholysis. The clinical correlation is that of small, flaccid blisters within the epidermis. Acantholysis occurs in situations with structural defects in desmosomal proteins such as is seen in Darier’s disease and Hailey-Hailey disease. In the former, there is almost

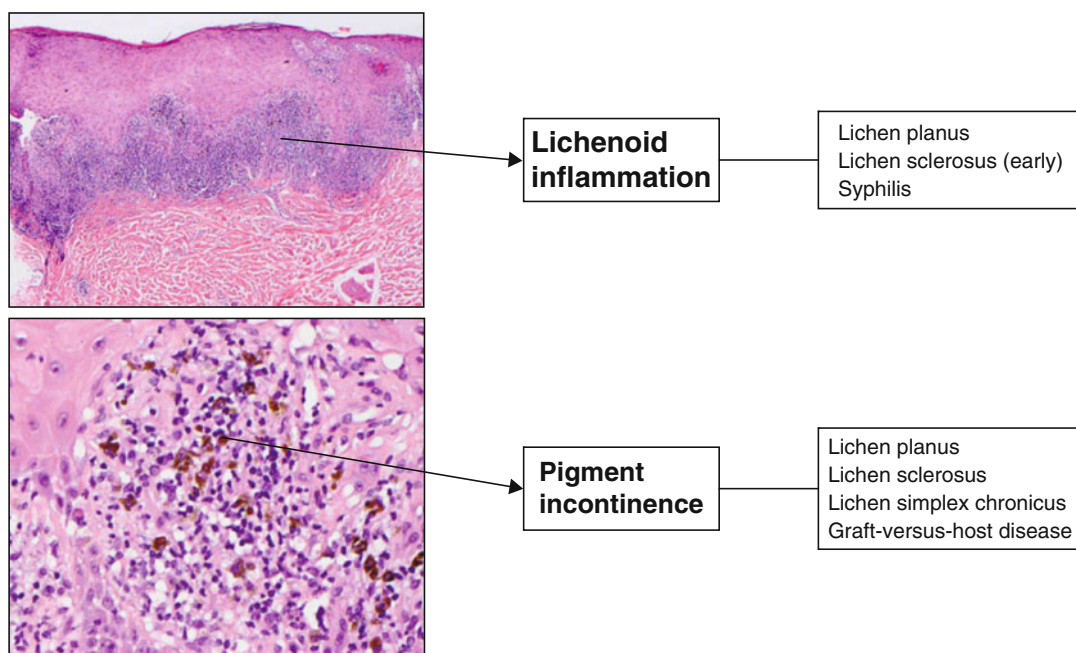


Fig. 2.5 In a lichenoid pattern, a band-like inflammation is seen in the superficial dermis

always extensive overlying orthokeratotic hyperkeratosis, while in the latter, spongiosis is usually quite prominent. Papular acantholytic dermatosis of the genitocrural area is an acantholytic disorder restricted to the genital area with a distinct clinical presentation. Acantholysis is also present in autoimmune diseases, such as in all types of pemphigus. Direct immunofluorescence is a very useful technique to establish this diagnosis. Acantholysis can also be encountered in herpetic dermatoses with other characteristic changes of viral infection. Rarely in the vulva, acantholysis may be seen in situations with cytological atypia such as in squamous cell carcinoma.

Reaction Pattern

Spongiotic Pattern

Spongiotic dermatitis is characterized by intraepidermal spongiosis (Fig. 2.1). A variety of conditions including contact or allergic dermatitis, drug eruption, and others will be discussed in Chap. 3.

Psoriasiform or Acanthotic Pattern

See acanthosis above (Fig. 2.2).

Interface Pattern

Interface dermatitis is defined as a lymphocytic infiltrate that extends into the epidermis resulting in basal vacuolization and focal necrosis of basal keratinocytes (Fig. 2.3). Focal spongiosis is often seen within the epidermis. Within the dermis, the lymphoid infiltrate involves the superficial vascular plexus. It is less confluent than is seen in lichenoid infiltrates and is associated with a different range of inflammatory disorders. Interface dermatitis does not have a discrete clinical correlate, though in extensive cases, subepidermal blistering may be present. The superficial lymphocytic infiltrate correlates with the clinical appearance of erythema. Interface dermatitis raises a differential diagnosis that includes lupus erythematosus and dermatomyositis (see Chap. 3). In lupus erythematosus, there is often orthokeratotic hyperkeratosis and a dense and peri-appendageal lymphoid infiltrate. In dermatomyositis, the inflammatory infiltrate is

generally less pronounced, not as deep and not peri-appendageal. Dermal mucin deposition may be extensive. Erythema multiforme and graft-versus-host disease may also demonstrate interface dermatitis. The presence of abundant papillary dermal edema and occasional neutrophils within the dermis may favor a fixed drug eruption. Early lesions of lichen sclerosis may demonstrate interface dermatitis or lichenoid dermatitis, often with overlying orthokeratotic hyperkeratosis.

ulosis, and irregular acanthosis of the epidermis (see Chap. 5). Lichen sclerosis, in its early and well-developed (but not late) stages, will demonstrate a lichenoid infiltrate, often with epidermal atrophy, overlying orthokeratotic hyperkeratosis, and dermal sclerosis. Syphilis is characterized by a band-like inflammatory infiltrate with psoriasiform epidermal hyperplasia. Usually, the other changes of a lichenoid process are not present and scattered plasma cells are present.

Lichenoid Pattern

Lichenoid dermatitis is similar to interface dermatitis. It is characterized by a band-like infiltrate within the papillary dermis that extends up into the epidermis resulting in focal necrosis of basal keratinocytes, basal vacuolization, and obscuring of the dermal epidermal junction (Fig. 2.4). There is no discrete clinical correlate to this histological finding and all observed clinical changes can be attributed to the concomitant histological changes. The prototypical lichenoid dermatosis is lichen planus that occurs with hyperkeratosis, hypergran-

Acantholytic and Blister Pattern

This pattern can exhibit blister below the stratum corneum, within the epidermis, or below the epidermis:

Intraepidermal Blister

See acantholysis (Fig. 2.6).

Subepidermal Blister

A subepidermal blister is a neat separation of the epidermis from the underlying dermis (Fig. 2.7). It may occur at several levels within

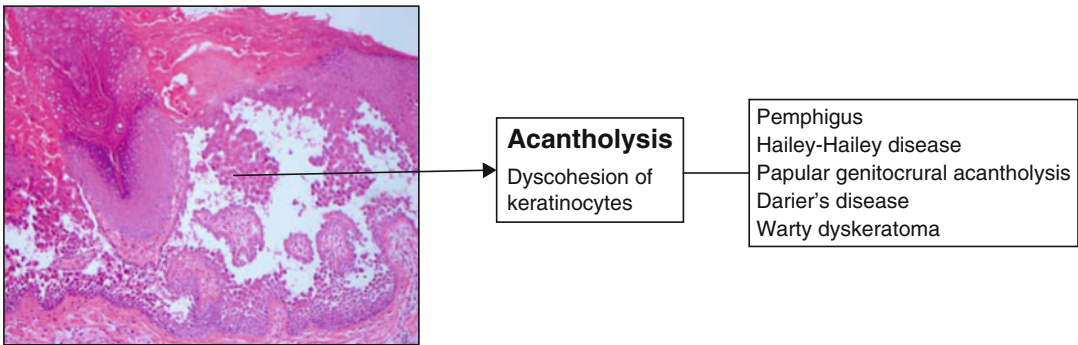


Fig. 2.6 Acantholytic pattern is an intraepidermal process

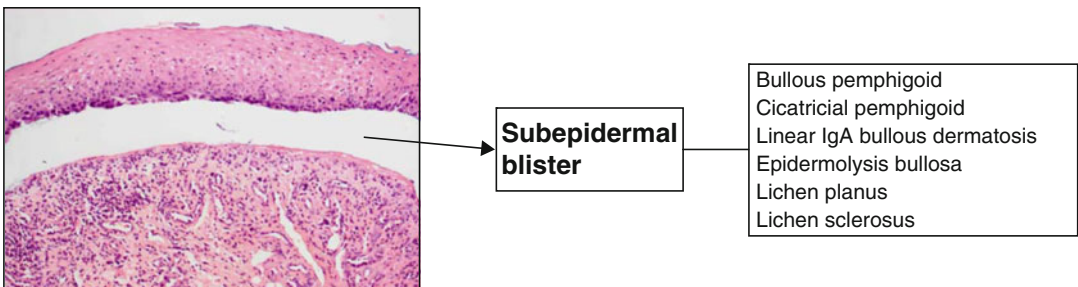


Fig. 2.7 A subepidermal blister pattern is shown here

the basement membrane zone, depending upon the pathogenesis of the blister (see Chap. 4). This separation that is evident on routine histological sections is apparent as a clinical blister. When subepidermal, blisters tend to be taut, tense, and remain intact. The presence of a non-inflammatory subepidermal blister may be suggestive of epidermolysis bullosa, an inherited mechanoblistering process. Subepidermal blis-

ters may occur in autoimmune blistering disorders such as IgA bullous dermatosis of childhood, cicatricial pemphigoid, and bullous pemphigoid. In these situations, there is a concomitant marked inflammatory infiltrate. Subepidermal blisters can also occur as a result of the marked destruction of basal keratinocytes such as is seen in lichen planus, lichen sclerosis, or erythema multiforme.

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